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June 18, 1999

Via facsimile, confirmation by first class mail

Elizabeth Dickinson, Esq.
U.S. FDA
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Rockville, Maryland 20855

Re: Petitions for Stay of Action Regarding Effective Approval of Any ANDA for a Generic Version of Platinol®-AQ
(FDA Docket Nos. 99P-1271 and 99P-1832)

Dear Liz:

We understand that you are presently considering the issue of 180-day exclusivity rights with respect to generic versions of Platinol®-AQ cisplatin injection. As you know, both American Pharmaceutical Partners, Inc. (successor to the generic pharmaceutical business of Fujisawa USA, Inc., hereinafter "APP") and Pharmachemie B.V., Inc. ("Pharmachemie") have submitted Petitions for Stay of Action with respect to this matter and those petitions have been assigned dockets numbers 99P-1271 (filed May 5, 1999) and 99P-1832 (filed June 9, 1999), respectively. APP's application for Platinol®-AQ has been assigned ANDA # 74-735 while Pharmachemie's application has been assigned ANDA # 74-656.

We believe that your resolution of the legal issues relating to this matter may be readily achieved by reference to both the applicable regulations and governing statutes. In essence, the Agency is faced with determining two issues, namely (1) whether Pharmachemie is entitled to any exclusivity, based upon its Paragraph IV certification with respect to now-expired U.S. Patent No. 4,310,515 ("the '515 patent") and (2) whether APP is entitled to exclusivity based upon its Paragraph IV submission with respect to U.S. Patent No. 5,562,925 ("the '925 patent").

99P-1271

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We believe that the question of whether Pharmachemie is entitled to exclusivity based upon its earlier certification concerning the '515 patent is simple and the conclusion is inescapable that Pharmachemie can have no exclusivity with respect to that certification. As a general principle, the '515 patent is expired (having expired on January 12, 1999) and under no possible scenario can a Paragraph IV certification regarding an expired patent afford any ANDA applicant exclusivity. In addition to the general logic of this conclusion, the applicable regulations and governing statutes confirm this logical result.

With respect to the expired '515 patent, all applicants should now have amended (or be in the process of amending) any prior certification concerning this patent to a Paragraph II certification acknowledging that the '515 patent has expired. We understand that APP has made, or is in the process of making, such a request. There is no prohibition against modifying a prior Paragraph IV certification to a Paragraph II certification. The only prohibition against modifications of prior Paragraph IV certifications relates to modifications to Paragraph III certifications, as discussed in 21 C.F.R. § 314.94(a)(12)(viii).

> (viii) *Amended certifications.* A certification submitted under paragraphs (a) (12)(i) through (a)(12)(iii) of this section may be amended at any time before the effective date of the approval of the application. However, an applicant who has submitted a paragraph IV patent certification may not change it to a paragraph III certification if a patent infringement suit has been filed against another paragraph IV applicant unless the agency has determined that no applicant is entitled to 180-day exclusivity or the patent expires before the lawsuit is resolved or expires after the suit is resolved but before the end of the 180-day exclusivity period. If an applicant with a pending application voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. An applicant shall submit an amended certification by letter or as an amendment to a pending application or by letter to an approved application . Once an amendment or letter is submitted, the application will no longer be considered to contain the prior certification.

Clearly, this provision is inapplicable to the present situation in which the modification is to a Paragraph II certification. Further, as provided in 21 C.F.R. § 314.94(a)(12)(viii), once an ANDA has been modified to remove a prior certification, that ANDA "will no longer be considered to contain the prior certification."

Accordingly, as to the expired '515 patent, APP's ANDA does not contain a Paragraph IV certification. This fact is dispositive with respect to the issue of Pharmachemie's alleged exclusivity. Pharmachemie's ANDA is not a previously submitted ANDA "containing a certification that the same patent was invalid, unenforceable, or would not be infringed," as required by 12 C.F.R. § 314.107(c)(1), the regulatory basis for the 180-day exclusivity period.

APP's application does contain a Paragraph IV certification as to the '925 patent, but this Paragraph IV is not relevant to Pharmachemie's alleged claim of entitlement to the 180-day exclusivity based upon the expired '515 patent. Determination as to which ANDA is "prior" with respect to the presently pending Paragraph IV certifications concerning the '925 patent is governed by 21 C.F.R. § 314.107(c)(2), which provides:

> (2) For purposes of paragraph (c)(1) of this section, the "applicant submitting the first application" is the applicant that submits an application that is both substantially complete and contains a certification that *the patent* was invalid, unenforceable, or not infringed prior to the submission of any other application for the same listed drug that is both substantially complete and contains *the same certification*.

Pharmachemie's ANDA did not contain *the same* Paragraph IV certification with respect to the '925 patent prior to APP's ANDA containing such a certification with respect that same patent. Pharmachemie admits such to be the case.

From the foregoing it should be clear that APP's ANDA for a generic version of Platinol®-AQ not only is free of any exclusivity in favor of Pharmachemie but is itself entitled to a period of 180-day exclusivity against all other ANDA applicants for this drug product.

With respect to the '925 patent, as the FDA records will show, and as confirmed by Pharmachemie in its own Petition (p. 2), APP was the first to submit a Paragraph IV certification with respect to that '925 patent. Pharmachemie is not entitled to any "relation back" benefit based upon its Paragraph IV certification with respect to the '515 patent. Pharmachemie's present Paragraph IV certification was submitted on or about February, 1997, over a month after APP filed such a Paragraph IV certification. Clearly, Pharmachemie in its original Paragraph IV certification with respect to the '515 patent, could not have certified with respect to the '925 patent *as the '925 patent did not issue until October, 1996*, long after Pharmachemie submitted its original Paragraph IV certification with respect to the now-expired '515 patent.

Pharmachemie's "relation back" argument in view of the *Granutec* decision is, of course, sheer nonsense. As the Agency is well aware, in the *Granutec* matter, the entity held to have the 180-day exclusivity, Genpharm, possessed a Paragraph IV certification that, as originally filed and later amended, related to the same patent. In contrast, there are two different Paragraph IV certifications over two different patents at issue in the present case.

Accordingly, APP is the first ANDA applicant for a generic version of Platinol®-AQ to have an ANDA for this drug product *containing a Paragraph IV certification for the '925 patent*. Thus, as provided by both FDA regulations and governing statutes, any ANDA containing such a subsequent Paragraph IV certification [subsequent to the date of APP's Paragraph IV certification for the '925 patent] may not be approved until 180 days after either (1) a court decision holding that the '925 patent to be either invalid or not infringed or (2) the marketing of the drug product by APP. The applicable regulation, 21 C.F.R. § 314.107(c)(1), further supports this conclusion:

> (c) *Subsequent abbreviated new drug application submission.* (1) If an abbreviated new drug application contains a certification that a relevant patent is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted *containing a certification that the same patent* was invalid, unenforceable, or would not be infringed and the applicant submitting the first application has successfully defended against a suit for

> patent infringement brought within 45 days of the patent owner's receipt of notice submitted under 314.95, approval of the subsequent abbreviated new drug application will be made effective no sooner than 180 days from whichever of the following dates is earlier:

(emphasis added) (underlined portion removed pursuant to the Interim Rule dated November 5, 1998, published in the Federal Register at 63 Fed. Reg. 59710 (Nov. 5, 1998)).

Pharmachemie's ANDA meets all of the foregoing criteria under 21 C.F.R. § 314.107(c)(1) such that FDA is precluded from approving this subsequent ANDA for the relevant 180-day period. Pharmachemie's ANDA is an ANDA that "contains a certification [as to the '925 patent] that a relevant patent is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted *containing a certification that the same patent* was invalid, unenforceable, or would not be infringed." As discussed previously, under applicable FDA regulations, APP's ANDA is an ANDA that was "previously submitted containing a certification that the same patent [the '925 patent] was invalid, unenforceable, or would not be infringed." In view of the cited regulations, APP, and not Pharmachemie, is entitled to 180 days of exclusivity.

The FDA regulations cited above are fully in accord with the governing statutes that require an analysis of the patent specific nature of Paragraph IV certifications. For example, 21 U.S.C. § 355(j)(2)(A)(vii) requires the submission of a patent certification, that is defined as follows:

> (vii) a certification, in the opinion of the applicant and to the best of his knowledge, *with respect to each patent* which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) and (c) of this section–
>
> (I) that such patent information has not been filed,
> (II) *that such patent* has expired,
> (III) of the date on which *such patent* will expire, or
> (IV) *that such patent* is invalid or will not be infringed
>
> by the manufacture, use or sale of the new drug for which the application is submitted:

(emphasis added).

Additionally, the statutory basis for the 180-day exclusivity period *requires* a patent specific analysis before one can determine settlement to the exclusivity period. 21 U.S.C. § 355(j)(5)(B)(iv) provides as follows:

> (iv) If the application contains *a certification described in subclause IV* of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification, the application shall be made effective not earlier than one hundred and eighty days after–

> (I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
>
> (II) the date of a decision of a court in an action described in clause (iii) *holding the patent which is the subject of the certification* to be invalid or not infringed, whichever is earlier.

(emphasis added). Accordingly, 21 U.S.C. § 355(j)(5)(B)(iv) requires one to refer back to the "certification described in subclause IV of paragraph 2(a)(viii)" to determine if there exists "a previous application [that] has been submitted under this subsection [containing] such a certification." In turn, subclause IV of paragraph 2(A)(viii) refers specifically to a certification "that such patent is invalid...."

In sum, applicable FDA regulations are in accord with the governing statutes – both that APP, not Pharmachemie, be accorded a 180-day period of exclusivity for a generic version of Platinol®-AQ.

Very truly yours,

LEYDIG, VOIT & MAYER, LTD.

By
Robert F. Green

RFG/krs